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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,176	09/02/2005	Klaus Sommermeier	3675.1001-0000	8000

21005 7590 03/12/2010
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EXAMINER

GOON, SCARLETT Y

ART UNIT

PAPER NUMBER

1623

MAIL DATE

DELIVERY MODE

03/12/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/537,176

Applicant(s)

SOMMERMEYER, KLAUS

Examiner

SCARLETT GOON

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-69 is/are pending in the application.
- 4a) Of the above claim(s) 54-68 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35-53 and 69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/GA-68)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date See Continuation Sheet

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :8 January 2910, 4 February 2010, 1 June 2005.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4 February 2010 has been entered.

DETAILED ACTION

This Office Action is in response to Applicant's Amendment and Remarks filed on 4 February 2010 in which claims 1-34 were previously cancelled, claims 35, 41, 54, 59, 63 and 68 are amended to change the scope and breadth of the claims, and claim 69 is newly added.

Claims 35-69 are pending in the instant application.

Claims 54-68 were previously withdrawn from further consideration in the Office Action dated 8 December 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Claims 35-53 and 69 are examined on its merits herein.

Priority

This application is a National Stage entry of PCT/EP03/13622 filed on 3 December 2003 and claims priority to Germany foreign application 10256558.9 filed on 4 December 2002. A certified copy of the foreign priority document in German has been received. No English translation has been received.

Information Disclosure Statement

The information disclosure statements (IDS) dated 8 January 2010 and 4 February 2010 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, they have been placed in the application file and the information therein has been considered as to the merits.

Furthermore, references B1, B2 and B3 on the IDS dated 1 June 2005 have also been considered as the relevance of these citations were disclosed in the International Search Report filed by Applicants.

Rejections Withdrawn

Applicant's amendment and arguments, filed 4 February 2010, with respect to the rejection of claims 35-53 under 35 USC § 112, second paragraph, as being indefinite for reciting "optionally substituted," have been fully considered and is persuasive because the amended claims no longer recite the phrase "optionally substituted."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Section [0001]

Claims 35-38, 41-44, 48, 49 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of EP 0605963 A2 to Wright (PTO-892, Ref. N), as evidenced by "WHO Food Additives Series No. 5" (of record).

Sommermeyer *et al.* teach compounds comprising a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxylalkyl starch is coupled to the active ingredient either directly or via a linker (paragraph 0029). HAS is preferably oxidized at the reducing end prior to binding to the active ingredient (paragraph 0031). Hydroxyethyl starch (HES) is the preferred HAS (paragraph 0050). HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch in a concentration of up to 95% (paragraph 0019). Any physiologically compatible HES can be used as the starting material, although HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134). HES preferably has a molar degree of substitution of 0.1 to 0.8 and a ratio of C₂:C₆ substitution in the range of 2 to 20 (paragraph 0134).

When HAS is bound to the active ingredient via a linker, the linker may be an amino acid, hydrazine or oxylamine derivative, among others (paragraph 0126).

It is noted that Sommermeyer *et al.* do not expressly indicate that HES used is the conjugation is amylopectin degradation fractions. However, as evidenced by the article entitled "WHO Food Additives Series No. 5" (of record), the molecular weight of waxy corn starch can be as high as 80,000,000. Therefore, since Sommermeyer *et al.* disclose that HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch (paragraph 0019) and preferably uses HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134), it is the Office's position that the HES described by Sommermeyer *et al.* is derived from amylopectin degradation fractions to obtain HES with an average molecular weight of 2 to 40 kD.

The teachings of Sommermeyer *et al.* differ from that of the instantly claimed invention in that Sommermeyer *et al.* do not disclose conjugation of oxidized HES to a linker wherein the end of the linker directly conjugated to HES forms an ester bond with oxidized HES upon conjugation.

Wright discloses water-soluble polymers that are modified to form a hydrazone linkage with an aldehyde group on a protein. Glycoproteins, i.e., polypeptides covalently joined to a carbohydrate molecule or molecules, provide additional opportunities for providing different methods of water-soluble polymer derivatization of a polypeptide because of the presence of the carbohydrate moieties on the polypeptide. Water-soluble polymer reagents may be coupled directly to the carbohydrate moieties of glycoproteins as opposed to the amino acid polypeptide backbone, i.e., various

functional groups present on the polypeptide, of the glycoprotein. It may be advantageous to couple water-soluble reagents to the carbohydrate moieties of the glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hindrance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified protein (p. 3, lines 38-46). Examples of water-soluble polymers (P) include, *inter alia*, dextran and dextran derivatives, cellulose and cellulose derivatives, starch and their derivatives, polyalkylene glycol and derivatives thereof, heparin and fragments of heparin (p. 7, line 54 – p. 8, line 16). Modified water-soluble polymers that are useful for conjugation to polypeptides include water-soluble polymers modified with a hydrazine or oxylamine group on the end of the linker to be conjugated to the polypeptide. The polypeptide is conjugated to the water-soluble polymer via an oxygen, as in, for example, formula (I) and formulas (XIX) – (XXVII), or a nitrogen linkage, as in, for example, formula (III) – (VIII) (p. 7, lines 19-53). The water-soluble polymer reagents, may be covalently attached to proteins through reactions with aldehyde groups introduced onto the carbohydrate moieties of the glycoprotein (p. 7, lines 5-18). The synthesis of hydrazine and oxylamine derivatives of water-soluble polymers are further exemplified wherein the water-soluble polymer is PEG (p. 12-18).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is

coupled to the active ingredient either directly or via a linker, with the teachings of Wright, regarding the conjugation of water-soluble polymers to polypeptides via a hydrazone linkage. As Sommermeyer *et al.* teach that when oxidized HAS is bound to the active ingredient via a linker, the linker may be, *inter alia*, an amino acid, hydrazine or oxylamine derivative, and Wright teaches hydrazine and oxylamine linkers for use in conjugation of water-soluble polymers to polypeptides, it would have been *prima facie* obvious for one of ordinary skill in the art to use the disclosed hydrazine and oxylamine linkers disclosed by Wright for conjugation of the peptide to oxidized HAS, with the expectation that it would yield a predictable result. It is noted that although Sommermeyer *et al.* teach that amino acids, hydrazides and oxylamines may be used as linkers for conjugation of oxidized HAS to an active ingredient, Sommermeyer *et al.* do not expressly indicate whether the hydrazide or oxylamine functional groups are directly conjugated to HAS or to the active ingredient. However, as Wright teaches that the hydrazide or oxylamine derivative can be conjugated to aldehyde groups introduced onto the carbohydrate moieties of the glycoprotein (active ingredient) rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hindrance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified protein, one of ordinary skill in the art would have been motivated to combine the teachings of Sommermeyer *et al.* with Wright, and prepare hydrazine and oxylamine derivatives as disclosed in Formulas (I) and (XIX)-(XXVII), wherein P represents oxidized HAS, with the expectation that the resultant HAS-hydrazine

derivative or HAS-oxylamine derivative could be used for conjugation to an active ingredient. Although not expressly taught, the combined teachings of Sommermeyer *et al.* and Wright suggest that the hydrazide and oxylamine derivatives of water-soluble polymers were purified in solution and concentrated to a solid form, thereby necessarily meeting the limitations of instant claims 48 and 49.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 35-38, 41-49 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record).

Sommermeyer *et al.* teach compounds comprising a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxylalkyl starch is coupled to the active ingredient either directly or via a linker (paragraph 0029). HAS is preferably oxidized at the reducing end prior to binding to the active ingredient (paragraph 0031). Hydroxyethyl starch (HES) is the preferred HAS (paragraph 0050). HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch in a concentration of up to 95% (paragraph 0019). Any physiologically compatible HES can

be used as the starting material, although HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134). HES preferably has a molar degree of substitution of 0.1 to 0.8 and a ratio of C₂:C₆ substitution in the range of 2 to 20 (paragraph 0134). When HAS is bound to the active ingredient via a linker, the linker may be an amino acid, hydrazine or oxylamine derivative, among others (paragraph 0126).

Sommermeyer *et al.* disclose in Example 2 (paragraph 0147) a compound wherein hydroxyethyl starch oxidized at the reducing end is reacted with HSA in the presence of EDC, in water. This is further exemplified in Table 2 (p. 11). Although not expressly indicated by Sommermeyer *et al.*, it is evidenced by Marder *et al.* that when an acid (i.e. oxidized hydroxyethyl starch) is reacted with EDC, an O-acylisourea intermediate, containing an ester linkage (compound (1) of Figure 1), is formed. When this reaction takes place in the presence of HOBt, a different ester (as defined by Applicant on p. 9 of the Specification) is formed, that between the acid and the hydroxyl group of HOBt (see compound (5) in Figure 1).

It is noted that Sommermeyer *et al.* do not expressly indicate that HES used is the conjugation is amylopectin degradation fractions. However, as evidenced by the article entitled "WHO Food Additives Series No. 5" (of record), the molecular weight of waxy corn starch can be as high as 80,000,000. Therefore, since Sommermeyer *et al.* disclose that HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch (paragraph 0019) and preferably uses HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134), it is the Office's

position that the HES described by Sommermeyer *et al.* is derived from amylopectin degradation fractions to obtain HES with an average molecular weight of 2 to 40 kD.

Although Sommermeyer *et al.* teach the activation of HES with EDC/HOBt prior to conjugation with HSA, Sommermeyer *et al.* do not teach that this activated ester intermediate is, or can be, isolated.

Hermanson teaches that EDC, a popular carbodiimide used in conjugation of biological substances, is labile in the presence of water (p. 170, section 1.1, paragraph 1). In the aqueous solutions, the oxygen atom of water can act as a nucleophile. Thus, hydrolysis of the O-acylisourea intermediate is a major competing reaction (p. 170, section 1.1, paragraph 2). An alternative is to use EDC in the presence of sulfo-N-hydroxysuccinimide (sulfo-NHS). Forming a sulfo-NHS ester intermediate from the reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activate carboxylate group to hours (p. 173, section 1.2, paragraph 2). Furthermore, EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, section 1.3, paragraph 3). A protein can be incubated in the presence of EDC/sulfo-NHS and the active ester form can be isolated. The isolated active ester is then mixed with a second protein or other amine-containing molecule for conjugation (p. 173, last paragraph). This two step process allows the active species to form only on one protein, thus gaining greater control over the conjugation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of

hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC. One of ordinary skill in the art would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Hermanson, that the reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activate carboxylate group to hours (p. 173, section 1.2, paragraph 2) and that this reaction usually increases the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, section 1.3, paragraph 3). Furthermore, one of ordinary skill in the art would have been motivated to combine the teachings and modify the conjugation procedure taught by Sommermeyer *et al.* such that the activated ester intermediate of HES is isolated prior to conjugation with HSA, in order to receive the expected benefit, as suggested by Hermanson, that sulfo-NHS activated ester complexes can be isolated before conjugation to another compound, thereby permitting greater control over the conjugation as only one reaction can occur to form the desired product rather than the formation of side products which can occur when intermediates are not isolated from their reaction conditions.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0003]

Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record), as applied to claims 35-38, 41-49 and 69, further in view of journal publication to Gunja *et al.* (of record), in view of journal publication by Mua *et al.* (of record).

The teachings of Sommermeyer *et al.*, Hermanson, Marder *et al.* and the publication by WHO were as disclosed in section [0002] above of the claim rejections under 35 USC § 103.

Sommermeyer *et al.* is silent with regards to the average branching of α -1,6-glycosidic linkages in the starch fractions.

Gunja *et al.* teach the enzymic conversion of amylopectin into glycogen-type polysaccharide. Table 2 shows that potato amylopectin has an average of 4-5% of α -1,6-glycosidic linkages (p. 1017, column 2). The introduction of the yeast branching enzyme further increases the branching by approximately 2-9% (p. 1017, column 2, last paragraph), resulting in a degree of branching of up to 14%.

Mua *et al.* teach the gel textural attributes of corn starch amylose and amylopectin fractions that vary in molecular weight and degree of branching. Starches isolated from different botanical sources have different functional properties and are used in foods and non-food products (p. 157, column 1). For amylopectin, the

molecular structure and degree of branching govern the starches' gel textural properties (abstract). Highly branched amylopectins exhibit decreased adhesive force and increased stringiness (p. 164, column 2). Knowing the relationships between the molecular structure and functional attributes of the starch could pave the way for new and improved starch uses (p. 157, column 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC, with the teachings of Gunja, regarding the use of a yeast enzyme to increase the degree of branching in amylopectin from 4-5% up to 14%, with the teachings of Mua *et al.*, regarding the influence branching has on the gelling properties of amylopectin. One of ordinary skill in the art would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Mua *et al.*, that the degree of branching can be used to affect the gelling properties of amylopectin. Thus, it is considered *prima facie* obvious for one of ordinary skill in the art to choose an amylopectin, with the appropriate degree of branching to yield a product with the desired gelling properties, for conjugation to a drug.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0004]

Claims 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record), as applied to claims 35-38, 41-49 and 69, further in view of journal publication to Nozaki *et al.* (PTO-892, Ref. U).

The teachings of Sommermeyer *et al.*, Hermanson, Marder *et al.* and the publication by WHO were as disclosed in section [0002] above of the claim rejections under 35 USC § 103.

The conjugation reaction mediated by EDC/HOBt, disclosed by Sommermeyer *et al.*, occurs in water. However, Hermanson teaches that an EDC conjugate is labile in the presence of water and thus can undergo hydrolysis. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art, a chemist, that it would be preferable have the aldonic acid ester in an aprotic organic solvent, such as DMF or DMSO, rather than in water, so as to avoid hydrolysis of the aldonic acid ester. Although discussed with a different carbodiimide, this point is further illustrated by Hermanson in saying that "active ester synthesis done...in an organic solvent...does not have the hydrolysis problems of water-soluble EDC-formed ester" (p. 178).

Nozaki *et al.* disclose peptide coupling reactions mediated by EDC and an additive in both aqueous media and in aprotic organic media. A comparison of three

additives, HOBt, HOSu (NHS), and HONbIt, and four different solvent conditions, DMF, 4:1 DMF/water, 1:4 DMF/water, and water were studied and the results of their coupling yield are disclosed in Table 1 (p. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC, with the teachings of Nozaki, regarding the use of additives, such as HOBt, HOSu and HONb in peptide coupling reactions mediated by EDC. Although Nozaki teach that peptide coupling reactions mediated by EDC and an additive can occur in an aqueous medium, in view of the teachings of Hermanson that an EDC conjugate is labile in the presence of water and thus can undergo hydrolysis, one of ordinary skill in the art would have been motivated to minimize the amount of water in the solvent, preferably using an aprotic organic solvent for the reaction, such as DMF as disclosed by Nozaki, with the expectation that the use of this solvent would minimize any potential hydrolysis reactions, and increase the reaction yield.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's amendment and arguments, filed 4 February 2010, with respect to the rejection of claims 35-38 and 41-53 made under 35 USC § 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view of Hermanson, as evidenced by Marder *et al.*, and the rejection of claims 39 and 40 made under 35 USC § 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view of Hermanson, as evidenced by Marder *et al.*, further in view of Gunja *et al.* and Mua *et al.*, have been fully considered but are not persuasive.

Insofar as Applicant's arguments are still applicable to the modified grounds of rejections presented above, Applicant argues that the reaction of HES, oxidized at the reducing end with EDC and HOBt according to Example 2 of Sommermeyer *et al.*, was performed in an aqueous solution. Although it was not disclosed whether this activation leads to an HES-ester with HOBt or not, it is well-known that such stable esters are only obtainable in anhydrous solvents, and that under the conditions disclosed in Example 2, a person skilled in the art would expect the formation of O-acylisourea which will immediately react with the protein. Applicant further argues that in contrast to the conditions used in Sommermeyer *et al.*, the esterification of the polysaccharide with HOBt in the instant application takes place in an anhydrous aprotic solvent. This argument is not persuasive because, contrary to Applicant's arguments, while stable esters with HOBt are typically obtained in anhydrous solvents, it is also known that such esters can be obtained in aqueous solvents, albeit at a lower yield. As disclosed in

Nozaki (PTO-892, Ref. U), conjugation of amino acids can occur in DMF alone, water alone, or a combination of DMF/water. As shown in Table 1, coupling efficiency increases in the presence of an additive in all solvent combinations tested. As such, contrary to Applicant's argument, a person skilled in the art would expect the formation of HES-esters in the aqueous solution of Sommermeyer *et al.* Furthermore, contrary to Applicant's argument, the instantly claimed invention does not take place in an anhydrous aprotic solvent, as this limitation is not recited in the independent claims. Moreover, dependent claim 51 indicates that the solvent can still contain up to 0.5% water, which is not anhydrous.

Applicant also argues that it would not be obvious to a person skilled in the art that the reaction of the sulfo-NHS with the EDC-activated complex would increase the yield of the coupling reaction dramatically because, contrary to the teachings of Hermanson *et al.*, Example 2 of Sommermeyer *et al.* shows that activation with HOBt reduces the yield, possibly encouraging secondary reaction, specifically citing "coupling C, table 2." Thus, Applicant argues that Sommermeyer *et al.* teach away from using HOBt as an activator. This argument is not persuasive. It is not readily apparent what part of Table 2 of the teachings of Sommermeyer *et al.* that Applicant is referring to as "coupling C," and how Applicant is coming to the conclusion that Example 2 shows that activation with HOBt reduces the yield. A careful analysis of Table 2 of the teachings of Sommermeyer *et al.* do not show the recitation "coupling C" anywhere within the Table, nor does Table 2 discuss anything with respect to the yield obtained from the various coupling reactions using Process A. References to a yield can be found in Table 1 of

the teachings of Sommermeyer *et al.*, but that yield is with respect to the oxidation reaction and not the conjugation reaction, and is therefore not relevant. Thus, it is maintained that in view of the teachings of Hermanson *et al.* that it would have been *prima facie* obvious for one of ordinary skill in the art to include HOBt or sulfo-NHS with the EDC-activated complex, in order to receive the expected benefit that HOBt and sulfo-NHS would increase the half-life of the activated group and would also increase the yield of the coupling reaction dramatically. Furthermore, one of ordinary skill in the art would have been motivated to isolate the HES-ester intermediate as Hermanson teaches that sulfo-NHS activated ester complexes can be isolated before conjugation to another compound. One of ordinary skill in the art would be aware that the isolation of an intermediate would permit greater control over the conjugation as only one reaction can occur to form the desired product rather than the formation of side products which can occur when intermediates are not isolated/purified from their reaction conditions.

Applicant further argues that according to the publication of Hermanson *et al.*, hydroxyl groups can react with the activated acids. However, Applicant further points to Example 6 of the teachings of Sommermeyer *et al.* to show that the use of HOBt and EDC does not lead to the self-condensation of HES, as would be expected. Applicant uses these teachings to argue that the instant invention surprisingly solves the problems associated with the use of carbodiimides, by overcoming the frequent inter- or intramolecular crosslinking reactions of the proteins as side effects. This argument is not persuasive because, as cited by Applicant, Example 6 of the teachings of Sommermeyer *et al.* show that no intra- or intermolecular crosslinking was observed

when the reactions were carried out in the presence or absence of HOBt. Applicants are also requested to note that secondary side reactions of intra- or intermolecular crosslinking is dependent on the nucleophilicity of the reacting compound. For example, in cases with proteins, it is common knowledge to one of ordinary skill in the art that an amino group is more nucleophilic than a hydroxyl group. Moreover, Hermanson teaches that isolation of the activated ester allows one to gain greater control over the resultant conjugated product. Thus, contrary to Applicant's arguments, the use of HOBt, NHS or sulfo-NHS in EDC-mediated conjugation reactions in the presence of aqueous and/or anhydrous aprotic solvents are *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35-38, 42-53 and 69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 61-79 of copending U.S. application no. 10/542,944.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to an aprotic-solvent soluble carbonic diester of HES, having a mean molecular weight in the range of 2000-300000 Da, a degree of substitution between 0.1 and 0.8, and a C2/C6 ratio of the substituents on the carbon atoms C2 and C6 of the anhydroglucoses between 2 and 15, and having a mean content of from 1:1 to 10:1 of carbonic diester substituents per HES molecule. The alcohol component from which the carbonic diester is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 64-66). The copending application is also drawn to a solid or solution comprising at least one of the disclosed carbonic diesters (claims 67 and 68). The solution comprises DMSO, DMF, DMS or N-methylpyrrolidone (claim 69). The copending application is also drawn to a method for production of HES carboxylic diesters, and a method of producing pharmaceutically active substances comprising reacting at least one HES carbonic diester with a pharmaceutical active substance.

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. The hydroxylalkyl starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol

group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS or N-methylpyrrolidone (claims 51-53).

Thus, the instant claims 35-38, 42-53 and 69 are seen to be anticipated by claims 61-79 of copending U.S. application no. 10/542,944.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 35-38 and 42-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15 and 16 of copending U.S. application no. 10/590,676.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the production of hyperbranched amylopectin. The method further includes a step of oxidizing the terminal reducing end of the hydrolysis product to the aldonic acid, and activating the aldonic acid group to the aldonic acid ester group. The Specification discloses that the aldonic acid ester group is derived from N,N'-disuccinimidyl carbonate.

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. They hydroxylalkyl

starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS and N-methylpyrrolidone (claims 51-53).

The claims of the copending application do not expressly disclose isolation of the aldonic acid ester or solid or solution comprising the aldonic acid ester. However, it would have been *prima facie* obvious to one of ordinary skill in the art to purify the aldonic acid ester prior to further reacting it with a pharmaceutical ingredient in order to minimize potential side reactions that may occur due to the use of impure reactants.

Thus, the instant claims 35-38 and 42-49 are seen to be obvious over claims 15 and 16 of copending U.S. application no. 10/590,676.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 35-38, 41-53 and 69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-22 of copending U.S. application no. 11/518,558.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for preparing a conjugate comprising a protein and a HAS polymer derivative. The HES has a molecular weight of from 2 to 200 kD. The method comprises selectively oxidizing the polymer at its reducing end and reacting the oxidized polymer with N,N'-disuccinimidyl carbonate at its oxidized reducing end to give a polymer derivative comprising a reactive carboxy group. The reactions are carried out in an anhydrous aprotic polar solvent, such as dimethyl acetamide or DMF (claim 22).

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. The hydroxylalkyl starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid

ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS and N-methylpyrrolidone (claims 51-53).

The claims of the copending application do not expressly disclose isolation of the aldonic acid ester or solid or solution comprising the aldonic acid ester. However, it would have been *prima facie* obvious to one of ordinary skill in the art to purify the aldonic acid ester prior to further reacting with protein to minimize potential side reactions that may occur due to impure reactants.

Thus, the instant claims 35-38, 41-53 and 69 are seen to be obvious over claims 16-22 of copending U.S. application no. 11/518,558.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 35-38, 41, 42 and 48-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 7,115,576 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a water-soluble antibiotic derivative represented by structural formula (I), wherein B may be HES, or soluble amylopectin in HES form. The mean molecular weight of the HES is in the range between 2000 and 200000 Da (claim 4). The HES displays a degree of substitution in the range of 0.3 to 0.5 (claim 8). The HES displays a C2/C6 substitution ration in the range of 2 to 12 (claim 9). The claims of the patent are also drawn to a method of preparing the water-

soluble antibiotic derivative represented by structural formula (II). The polysaccharide is oxidized at the reducing end (claim 17).

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. The hydroxyalkyl starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS and N-methylpyrrolidone (claims 51-53).

Thus, the instant claims 35-38, 41, 42 and 48-53 are seen to be anticipated by claims 1-32 of U.S. Patent No. 7,115,576 B2.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Although not currently cited in the rejections, Applicant is

respectfully requested to note that any rejection over WO 2002/080979 is equally applicable to DE 10112825 A1.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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